Paper No. 29

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte JEFFREY C. GEESIN and
ANNA GOSIEWSKA

Appeal No. 2002-1296
Application No. 08/957,038

ON BRIEF

Before WILLIAM F. SMITH, SCHEINER, and GRIMES, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 15 through 21, all the claims remaining in the application. Claim 15 is representative of the subject matter on appeal and reads as follows:

15. A method for identifying modulators of scar formation, comprising the steps of:

(a) incubating immortalized, non-cancerous macrophages with an exogenous source of latent TGF-β1 and a modulator compound that modulates latent TGF-β1 activation;

(b) measuring the amount of active TGF-β1 produced by the macrophages; and

(c) comparing the measured amount of active TGF-β1 produced in step (b) with a control, the control being the measured amount of active TGF-β1 produced by the incubation of step (a) without the modulator compound of step (a) in order to identify the modulator compound's propensity for scar formation.

The references relied upon by the examiner are:

Purchio et al. (Purchio) 5,844,085 Dec. 1, 1998

Twardzik et al. (Twardzik), "γ-Interferon-Induced Activation of Latent Transforming Growth Factor-β by Human Monocytes," Annals New York Academy of Sciences, Vol. 593, pp. 276-84 (1990)

ATCC Cell Lines & Hybridomas, Eighth Ed., American Type Culture Collection, ISBN: 0930009541, p. 337 (eds. Hay et al., 1994)

Adams, "Macrophages," Cell Culture, Vol. 58, Chapter 43, pp. 494-506 (eds. Jacoby et al., Academic Press, March 1979)

Huber, et al. (Huber), "Activation of Human Platelet-Derived Latent Transforming Growth Factor-β1 by Human Glioblastoma Cells," Biochem. J., Vol. 277, pp. 165-177 (July 1, 1991)

Flaumenhaft et al. (Flaumenhaft), "Activation of Latent Transforming Growth Factor β," Adv. Pharmacol., Vol. 24, pp. 51-76 (1993)

Beauchamp et al. (Beauchamp), "Phenotypic Alterations in Fibroblasts and Fibrosarcoma Cells that Overexpress Latent Transforming Growth Factor-β1," Endocrinology, Vol. 130, No. 5, pp. 2476-86 (1992)

Nunes et al. (Nunes), "Characterization of Latent TGF-β Activation by Murine Peritoneal Macrophages," J. Immunol., Vol. 155, No. 3, pp. 1450-59 (August 1, 1995)

Claims 15 through 21 stand rejected under 35 U.S.C. § 103(a). As evidence of obviousness, the examiner relies upon various combinations of the references listed above. We reverse.

Background

The present invention involves Transforming Growth Factor-β. As explained by the specification:

> Transforming Growth Factor B (TGF-β) is a potent growth regulatory protein and a key molecule implicated in various fibrotic (scarring) disorders. Most of the cells secrete TGF-β1 in a predominantly inactive high molecular weight form, latent TGF-β (L-TGF-β). Latent TGF-β is composed of an amino-terminal latency-associated peptide (LAP) noncovalently associated with the carboxyl-terminal mature TGF-β. The latency-associated peptide, is disulfide-bonded to a second, structurally unrelated protein, latent TGF-β binding protein (LTBP), which plays a role in the processing and secretion of TGF-β (1).
>
> A major mechanism of regulating TGF-β activity occurs through factors which control the processing of the latent to biologically active form of the molecule. Physiochemical activation can occur by extremes of pH, heat, chaotropic agents (sodium dodecyl sulfate, urea) and deglycosylation (2, 3, 4, 5). Activation in vivo is more complex and not well understood.

Id., page 1, first and second paragraphs. Since active TGF-β1 is involved in scarring and fibrotic disorders, agents which sustain the latency of TGF-β1 would be expected to be useful as anti-fibrotic and anti-scarring agents. Id., pages 2-3.

The assay set forth in claim 15 on appeal is designed to identify compounds that modulate latent TGF-β1 activation. An important aspect of the assay is the use of immortalized, non-cancerous macrophages in step (a). Appellants contrast the present assay with a prior art assay described as a co-culture system stating:

> The method of the present invention is simple and is based on homotypic cell culture. In contrast, in the co-culture model, two cell types must be present and a number of requirements have to be fulfilled. The cell types must be either in contact or in very close proximity in order to produce active TGF-β1 since the co-culturing of endothelial cells on a surface 1-2 mm above a monolayer of smooth muscle cells fails to produce active TGF-β1. A strong species specificity appears to exist as bovine arterial endothelial cells do not activate latent TGF-β1 in the presence of either human or pig smooth muscle cells. The sensitivity of this method of the present invention could be manipulated since the source of latent TGF-β1 which is activated by macrophages is not limited to fibroblast conditioned

> media. Recombinant latent TGF-β1 was converted to active form as well. One major disadvantage of the co-culture system is lack of reproducibility. Large numbers of BAEC and SMC cell clones need to be screened in order to develop an effective method. This requires isolation of a number of cell clones and subsequent laborious testing since the cells, after several population doublings, need to be replaced. In contrast, transformed macrophages as used in the present invention are capable of continuous culture and are readily available for routine analysis.
>
> Another limitation of the co-culture model is the fact that this system fails to produce active TGF-β1 in the presence of LPS in the tissue culture medium derived from the water or calf serum. It was reported that LPS found in the tissue culture medium downregulated the mRNA levels for TGase II and TGF-β1 in bovine arterial endothelial cells. This creates a need for testing each batch of tissue culture medium and serum for the presence of LPS in order to generate active TGF-β1. In contrast, the present disclosure showed that LPS-induced macrophages expressed higher levels of TGase II than untreated cells. This may indicate the LPS induces the activation of TGF-β1 through upregulation of TGase II levels in macrophages whereas it suppresses the activation of TGF-β1 by downregulation of TGase II in endothelial cells. It is also apparent that the method of the present invention is more versatile than the co-culture system.

Id., pages 23-24 (reference citations omitted).

Discussion

The rejection of claim 15 is premised upon Purchio, Twardzik, ATCC, Adams, Huber, and Flaumenhaft. In reviewing the matter, it appears that Purchio and Twardzik in relevant part describe the same work. We note that Purchio is a co-author of the Twardzik publication and Twardzik is a co-inventor of the Purchio patent. Furthermore, the specific disclosure of Purchio relied upon by the examiner, i.e., column 64, line 44 - column 66, line 51, is also reported in Twardzik. Also, the most specific information the examiner relies upon from Twardzik, i.e., its recognition of "the equivalence of monocytes and macrophages" (Examiner's Answer, page 5), is also found in Purchio

when it is considered that the monocytes used in Purchio are macrophages which circulate in the blood. Thus, we shall focus our attention on Purchio.

Purchio describes an assay similar to that required by claim 15 on appeal in that human macrophages (monocytes) are cultured in the presence of recombinant gamma interferon (rγINF) and latent TGF-β1 (LnTGF-β1). A control assay using macrophages and LnTGF-β1 is also described. See Purchio, column 65, line 24 - column 66, line 51, especially Table XIII. The data show that rγINF induced increased activation of LnTGF-β1 by human macrophages. As explained:

> These results indicate that γINF effectively induces human monocytes to mediate the release of active TGF-β from a latent recombinant TGF-β complex. The TGF-β released into supernatants, derived from exogenously added LnTGF-β1, appears to be both functionally identical with TGF-β1 (mAb neutralization of NRK colony formation) and exhibits a mass (SDS-PAGE) identical to natural TGF-β isolated after purification at acid pH from platelet and bone.

Id., column 66, lines 43-50.

Since rγINF served to modulate release of active TGF-β1 from LnTGF-β1 in the assay of Purchio, it appears reasonable to denominate rγINF a "modulator compound" as required by claim 15 on appeal. Thus, the question becomes would it have been obvious to one of ordinary skill in the art to use immortalized, non-cancerous macrophages in the assay described in Purchio? The examiner relies upon ATCC, Adams, Huber, and Flaumenhaft as evidence to support this modification. We agree with appellants that these references do not provide sufficient evidence to support the proposed modification.

ATCC provides evidence that one of appellants' preferred immortalized, non-cancerous macrophages, mouse peritoneal macrophages IC-21 transformed with

SV-40, was known in the art, stating that this cell line is a "valuable model in the study of macrophage properties and activities." Id., page 337. The examiner relies upon Adams for its disclosure that macrophage cell lines are easy to grow and are passaged without difficulty. Examiner's Answer, page 5. Huber is concerned with the activation of LnTGF-β1 by human glioblastoma cells and is relied upon for suggesting "the addition of exogenous forms of latent TGF-β to cell cultures in order to study latent TGF-β activation mechanisms." Id., pages 5-6. Flaumenhaft is relied upon for its disclosure that an understanding of the regulation of TGF activity will allow effective interference with inappropriate TGF-β activity. Id., pages 67-68; Examiner's Answer, page 6. The examiner concludes:

> ... it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to stimulate macrophages with γINF and incubate them with exogenous LnTGF-β, as taught by Purchio and Twardzik, and to modify that teaching by substituting IC-21 cells, as taught by ATCC Cell Lines & Hybridomas, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because IC-21 cells share many characteristics with normal peritoneal macrophages and are thus a valuable model in the study of macrophage properties and activities. Activation of LnTGF-β is an activity of macrophages. Macrophage ce
> passaged without difficulty. They offer the obvious advantage of providing large numbers of cells with minimal difficulty. One of ordinary skill in the art would be motivated to study this activation in the presence of a modulator compound in order to elucidate physiological mechanisms of activation of LnTGF-β or to understand how the activation of latent TGF-β is controlled. The invention is prima facie obvious over the prior art.

Examiner's Answer, paragraph bridging pages 6 and 7.

As argued by appellants, the macrophages used in Purchio are of finite life span and would create an uncontrolled variable if the assay described in Purchio was used to screen compounds as putative modulators of latent TGF-β1 activation. Appeal Brief, page 6. The examiner has correctly found that appellants' preferred immortalized, non-cancerous macrophages, the IC-21 cell line, were known at the time of the present invention. The examiner is also correct in finding that Huber and Flaumenhaft suggest studying the activation of TGF-β so that an understanding of TGF activity may be had which may allow effective interference with inappropriate TGF-β activity. However, the references relied upon by the examiner that are directed to studying the activation of TGF-β, use macrophages, not immortalized, non-cancerous macrophages as required by the claims on appeal. The mere existence of cell lines such as IC-21 does not in and of itself suggest modifying the assay described in Purchio in the manner required to arrive at the subject matter set forth in the claims on appeal. The “motivation” identified by the examiner, the desire to “to elucidate physiological mechanisms of activation of LnTGF-β or to understand how the activation of latent TGF-β is controlled,” would be accomplished simply by following the references’ methods which use macrophages. On this record, the only reason, suggestion, or motivation to modify Purchio in the manner proposed by the exmainer comes from appellants' disclosure of the present invention, not from the teachings of the applied references.

The decision of the examiner is reversed.

REVERSED

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William F. Smith	)
Administrative Patent Judge	)
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	) BOARD OF PATENT
Toni R. Scheiner	)
Administrative Patent Judge	) APPEALS AND
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	) INTERFERENCES
Eric Grimes	)
Administrative Patent Judge	)

Audley A. Ciamporcero, Jr.
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003

dem